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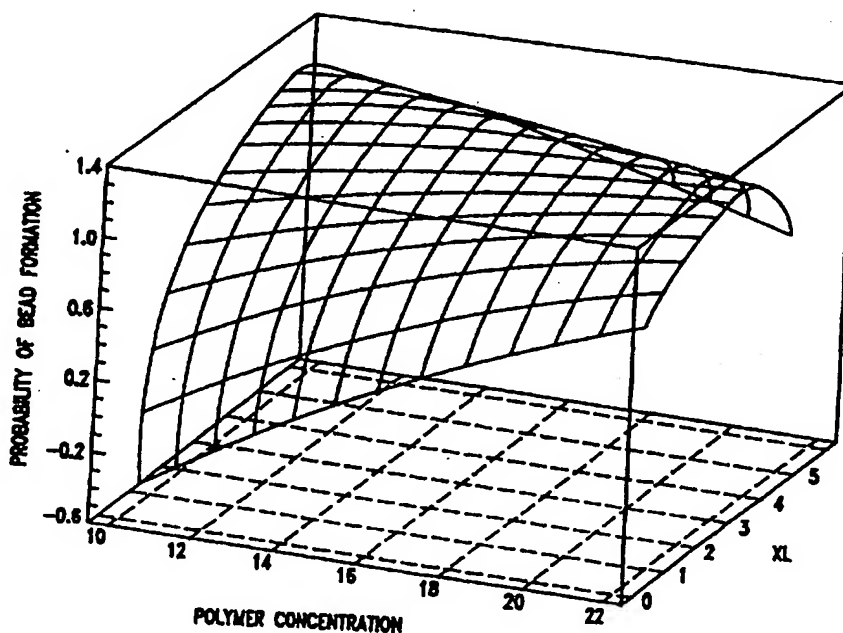
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(54) Title: RESPONSIVE POLYMER GEL BEADS

(57) Abstract

A responsive gel bead is provided, which includes a polymer in the form selected from the group consisting of individual polymers, polymer blends and interpenetrating polymer networks, which is chemically cross-linked with a bi-functional or multi-functional organic compound, the gel bead having an LCST of less than 55 °C. The responsive gel bead additionally possesses a diameter in a collapsed state of less than 600 µm, the collapsed state at a temperature no greater than 75 °C, and is capable of absorbing at least 5 grams solvent per milliliter of collapsed gel. A method for the manufacture of the responsive cellulosic gel beads by inverse suspension cross-linking includes providing an aqueous suspension of a cellulose ether polymer, an organic solvent and a cross-linker, where the organic solvent is immiscible with the aqueous suspension and admixing the aqueous cellulose ether suspension, the organic solvent and the cross-linker to form a two-phase system, where the aqueous suspension and the organic solvent comprise the two phases of the system. Surfactants, compatibilizing agents and other additives may be desirable. The two-phase system is agitated sufficient to form droplets of the aqueous cellulose ether suspension in the organic solvent and maintained for a time sufficient to form cross-linked cellulose ether gel beads. The cross-linked cellulose ether gel beads are recovered from the organic solvent.



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RESPONSIVE POLYMER GEL BEADS

This application is a continuation in part application of co-pending application U.S.S.N. 08/276,532, filed July 18, 1994 and entitled "Useful
5 Responsive Polymer Gel Beads", herein incorporated by reference.

Background of the Invention

Volumetric change phenomena have been observed in crosslinked polymer gel networks. As an external environmental condition (e.g.,
10 temperature; solvent composition; pH; electric field; light intensity and wavelength; pressure; ionic strength, etc.) is changed, the polymer network contracts and/or expands in volume (i.e., the gel is a "responsive" gel). The volume of such a gel may, under certain circumstances, change reversibly by a factor as large as several hundred when the gel is presented with a
15 change in external conditions. See, Tanaka *Phys. Rev. Lett.* **40**(12), 820-823 (1978); Tanaka *et al.*, *Phys. Rev. Lett.* **38**(14), 771-774 (1977); *Phys. Rev. Lett.* **45**(5), 1636 (1980); Ilavsky, *Macromolecules* **15**, 782 (1982); Hrouz *et al.*, *Europ. Polym. J.* **17**, 361 (1981); Ohime *et al.* *J. Chem. Phys.* **8**, 6379 (1984); Tanaka *et al.* *Science* **218**, 462 (1982); Ilavsky *et al.* *Polym. Bull.* **7**, 107 (1982); Gehrke, "Responsive Gels: Volume Transitions II";
20 Editor: K. Dusek Springer-Verlag New York, New York, pp. 81-144 (1993); Li *et al.* *Annual Rev. Mater. Sci.* **22**, 243-77 (1992); and Galaev *et al.* *Enzyme Microb. Technol.* **15**, 354-66 (1993), all of which are incorporated by reference.

25 Investigators have reported the formation of responsive gels using a variety of polymer networks, including certain acrylamides, acrylates, polysaccharides and synthetic polymers, such as polyvinylalcohol (PVA) and polyethyleneoxide (PEO). Preparation of responsive gels as a bulk slab or flakes has been reported; however, it is desirable to make responsive gels in
30 the form of beads. The spherical shape of the beads permits more uniform

control of swelling and contraction. The beads readily lend themselves to separation processes and/or can be synthesized into a particular size to best suit a particular application and to control properties which are particle size related. Additionally, beads allow close packing and uniform free volume
5 allowing easy measurement of swelling and compression.

Because swelling of a responsive gel is diffusion controlled, the responsive gel bead is desirably of relatively small diameter, thereby reducing the amount of time required to swell the gel bead. Desirably, the responsive gel bead also is capable of rapid swelling by absorbing solvents
10 and collapsing by the subsequent expulsion of entrained solvent. ("Solvents" as used herein include water, pure solvents, mixed solvents and/or solutions. Such solutions may also be saline, acidic or base, contain ions and/or contain particulate matter). Further, a desirable responsive gel bead may be capable of absorbing significant amounts of solvent. Lastly, it is desirable
15 that the gel bead have a lower critical transition temperature (LCST) not significantly above room temperature in order to permit energy efficient cycling of the gel between the swollen and collapsed states.

Preparation of *N*-isopropylacrylamide responsive gel beads has been reported by emulsion or suspension polymerization. See, Hirose *et al.*
20 *Macromolecules* 20, 1342-4 (1987); U.S. Patent No. 5,183,879 to Yuasa *et al.*; and JP 90-260558 to Kohjin Co., Ltd., all of which are incorporated herein by reference. In such suspension polymerization reactions, monomer droplets are dispersed into an immiscible phase and polymerization of the monomer droplets is initiated. There are several reasons, however, why one
25 would prefer not to prepare responsive gel beads from monomers. Firstly, those monomers known to provide responsive gels, such as acrylamide and acrylate are highly toxic, mutagenic and carcinogenic. In comparison, the corresponding polymers, i.e., polyacrylamides and polyacrylates, are significantly less toxic. Indeed, many natural polymers, such as
30 polysaccharides, actually are biocompatible. In addition, beads of *N*-

isopropyl acrylamide may be mechanically weak and do not have the mechanical integrity to survive in demanding environments. Secondly, preparation of a polymer network starting from a polymer permits greater reaction control, since one can select polymers of known composition and molecular weight. Polymer formation is no longer a variable in the formation of the polymer gel network.

Although there is an interest in preparing responsive polymer crosslinked gel beads, little of their preparation has been reported. U.S. Patent No. 3,208,994 to Flodin *et al.* (which is incorporated herein by reference) generally discloses a method of preparing gel beads of a wide range of polysaccharides using a technique known as suspension crosslinking. Flodin *et al.* report the introduction of a water hydrated polysaccharide and crosslinker into a suspension medium under agitation so as to obtain suspended drops of the polysaccharide suspension. Flodin *et al.* disclose the use of epichlorohydrin as the crosslinker and an aromatic hydrocarbon or a halogenated hydrocarbon as the suspension medium. While Flodin *et al.* report the formation of gel beads using ethylhydroxyethyl cellulose (EHEC), now realized to have responsive characteristics, the method of Flodin and the beads produced are not useful nor, indeed, were they ever intended to be useful as responsive beads, in terms of the objectives of the invention reported here. The synthetic method of Flodin *et al.* involves solvents and quantities of crosslinkers that have proven not commercially useful due to economic and environmental considerations. In addition, Flodin *et al.* do not produce beads which meet several of the commercially important objects of this invention, namely presence of an LCST not significantly above room temperature and has not been demonstrated to meet several of the other objects, namely rapid swelling and collapse in response to environmental stimuli and absorption and desorption of a large volume of solvent per milliliter of collapsed gel. Further, the applicants have recently become aware of attempts by others to

prepare hydroxypropyl cellulosic (HPC) gel beads (a responsive gel) by introducing the aqueous HPC solution into toluene, according to the general method disclosed by Flodin *et al.* Such attempts were reported to have been unsuccessful (private communication, Stevin Gehrke).

- 5 It is a further object of the present invention to provide a responsive gel bead which is mechanically strong. It is further object of the present invention to provide a responsive gel bead which is manufactured using methods and solvents which are economical and environmentally safe. Any specific application may be best served by selection of a specific responsive
- 10 gel polymer whose characteristics most closely meet the needs of the application. Thus, there remains a need to produce gel beads of a wide variety of responsive gel polymers. In particular, a method of producing cellulosic gel beads, and more particularly HPC gel beads, is desired.

15 **Summary of the Invention**

- The present invention provides a responsive gel bead possessing desirable performance characteristics under specific operating conditions wherein the selection of the desired polymer is based in part on factors unrelated to gel bead form and size. An object of the present invention is to
- 20 provide a responsive gel bead of small diameter possessing desirable performance characteristics. A further object of the present invention is to provide a responsive gel bead capable of rapid swelling and collapse in response to environmental stimuli. It is yet a further object of the present invention to provide a responsive gel bead capable of absorbing a large
- 25 volume of solvent per milliliter of collapsed gel. It is a further object of the invention, to provide a responsive gel bead having an LCST at not significantly above room temperature. It is yet a further object of the present invention to provide a responsive gel bead, more particularly, a responsive cellulosic gel bead, and more particularly a responsive HPC gel
- 30 bead, having one or more of the above-stated properties.

The present invention is a responsive gel bead obtainable from a specific method of inverse suspension crosslinking of a polymer. In particular, the present invention may be a responsive cellulosic gel bead obtainable under particular process conditions from the inverse suspension crosslinking of a cellulose ether.

In one aspect of the invention, a responsive gel bead includes a polymer which is chemically crosslinked with a bi-functional or multi-functional organic compound, the gel bead having an LCST of less than 55°C. The polymer may be an individual polymer, a polymer blend or an interpenetrating polymer network. In preferred embodiments, the responsive gel bead may have a diameter in a collapsed state of less than 600 μm , the collapsed state at a temperature of no greater than 75°C. The ratio of a mean diameter of the gel bead to a median diameter of the gel bead is preferably no more than 1.2 in a collapsed state. The responsive gel bead may also be capable of absorbing at least 5 grams solvent per milliliter of collapsed gel, wherein the collapsed gel is at a temperature of no greater than 75°C. The responsive gel bead may also be capable of responsively absorbing at least 5 gram solvent per milliliter of collapsed gel in one hour or less, or absorbing and releasing at least 5 gram solvent per milliliter of collapsed gel in two hour or less, wherein the collapsed gel is at a temperature no greater than 75°C.

In another aspect of the invention, a responsive cellulosic gel bead includes a cellulose ether polymer which is chemically crosslinked with a bi-functional or multi-functional organic compound, the gel bead having an LCST of less than 55°C. The cellulose ether polymer may be an individual polymer, a polymer blend or an interpenetrating polymer network. In preferred embodiments, the responsive cellulosic gel bead may have a diameter in a collapsed state of less than 600 μm , the collapsed state at a temperature of no greater than 75°C. The ratio of a mean diameter of the gel bead to a median diameter of the cellulosic gel bead is preferably no

more than 1.2 in a collapsed state. The responsive cellulosic gel bead may also be capable of absorbing at least 5 grams solvent per milliliter of collapsed gel, wherein the collapsed gel is at a temperature of no greater than 75°C. The responsive cellulosic gel bead may also be capable of
5 responsively absorbing at least 5 gram solvent per milliliter of collapsed gel in one hour or less, or absorbing and releasing at least 5 gram solvent per milliliter of collapsed gel in two hour or less, wherein the collapsed gel is at a temperature no greater than 75°C.

In another aspect of the present invention, a responsive gel bead
10 includes a preformed polymer which is then chemically crosslinked with a bi-functional or multi-functional organic compound, the gel bead having a diameter of less than or equal to 400 μm as prepared and measured at a temperature of less than 30°C. The responsive gel bead may also includes a preformed polymer which is then chemically crosslinked with a bi-functional
15 or multi-functional organic compound, the gel bead having a diameter of less than or equal to 50 μm as prepared and measured at a temperature of less than 30°C.

In preferred embodiments, the responsive cellulosic gel bead includes hydroxypropyl cellulose (HPC) and methyl cellulose (MC), and mixtures
20 thereof, optionally blended with hydroxyethyl cellulose (HEC), carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC), ethylhydroxyethyl cellulose (EHEC), hydroxymethyl cellulose (HMC), and methylhydroxyethyl cellulose (MHEC) and mixtures thereof. The responsive cellulosic gel is preferably a responsive HPC gel, having an
25 LCST of between 42° and 46°C.

In another aspect of the invention, a method for the manufacture of particular desirable responsive gel beads under specific reaction conditions by inverse suspension crosslinking is provided. Accordingly, an aqueous polymer suspension, an organic solvent and a crosslinker are provided and
30 admixed to form a two-phase system, where the aqueous suspension is

immiscible in the organic solvent so as to make up two phases. The two-phase system is agitated sufficient to form droplets of aqueous polymer suspension in the organic solvent. The agitation of the two-phase system is maintained for a time sufficient to form crosslinked polymer gel beads and
5 the crosslinked polymer gel beads are thereafter recovered from the organic solvent.

In preferred embodiments, the organic solvent is a hydrocarbon selected from the group consisting of paraffinic hydrocarbons, petroleum-based hydrocarbons, high purity mineral oils and mixtures thereof. The fine
10 mineral oil preferably has a viscosity less than 2 cSt. In other preferred embodiments, the organic solvent is selected from the group consisting of decane, octane, nonane, undecane, dodecane, straight chain paraffinic and petroleum-based hydrocarbons and mixtures and blends thereof. The organic solvent may include a cycloalkane, such as cyclohexane and decalin.

15 In another preferred embodiment, a compatibilizing agent may be admixed into the organic solvent. A "compatibilizing agent", as that term is used herein, means a polymer, oligomer or compound that is substantially non-reactive to the components of the crosslinking polymerization system and which includes both hydrophilic and hydrophobic regions. The
20 compatibilizing agent may include an intermixture of hydrophobic and a hydrophilic regions. The compatibilizing agent may include a copolymer of a hydrophilic monomer and a hydrophobic monomer. By "intermixture", as that term is used herein, it is meant a compatibilizing agent which includes a mixture of both hydrophilic and hydrophobic regions. The mixture may be
25 that of individual compounds, i.e., mixtures of molecules having either hydrophobic or hydrophilic character, or of subcomponents which together make up a oligomer or polymer, i.e., block co-polymer of hydrophobic and hydrophilic monomers.

The beads of the present invention can be used in any application by
30 modifying the bead properties to those required by its intended use. The

responsive gel beads of the present invention may be of small diameter, rapidly responsive, highly absorbent and/or responsive at temperatures near room temperature. Further, the method of the present invention, provides a reliable and efficient route for making the responsive gel beads with
5 desirable properties.

Brief Description of the Drawing

The novel features of the invention both as to its structure and operation are best understood from the accompanying drawing, taken in
10 conjunction with the accompanying description, in which:

The Figure is a responsive surface plot illustrating the effect of crosslinker level and polymer concentration on bead formation.

Detailed Description of the Preferred Embodiment

15 The present invention is based upon the discovery that cellulosic gel beads having a relatively low LCST and one or more of the desirable properties of small size, rapid response and high absorptivity may be prepared by suspension crosslinking under controlled reaction conditions of an aqueous cellulose suspension dispersed in a continuous organic phase.
20 The applicants further have discovered that cellulosic gel beads advantageously may be made by introducing the water hydrated cellulose ether into a high purity fine mineral oil.

In one aspect of the invention, a responsive gel bead includes a polymer which is chemically crosslinked with a bi-functional or multi-
25 functional organic compound, the gel bead having a lower critical solution temperature (LCST) of less than 55°C. The polymer may be an individual polymer, polymer blend or an interpenetrating polymer network.

By "lower critical solution temperature", as that term is used herein, it is meant the temperature below which a polymer is substantially soluble in
30 a liquid and above which the polymer is substantially insoluble and therefore

forms a two phase system. The transition from solubility to insolubility is termed a "phase transition". The LCST of responsive cellulosic gels is well known and can be easily determined and verified. Exemplary LCST's (degrees C) are 42°-46° (hydroxypropyl cellulose; HPC), 59°
5 (hydroxypropylmethyl cellulose; HPMC), 49°C (methyl cellulose; MC), 60° (methylhydroxyethyl cellulose; MHEC), and 55°-70° (ethylhydroxyethyl cellulose; EHEC). It is anticipated that the LCST of the gel bead is normally comparable to that of the bulk gel. The LCST of a bulk gel may be lowered or raised by the addition of a hydrophilic, hydrophobic, or ionic
10 element. "LCST" as used herein encompasses bulk LCST, modified LCST and LCST affected by ionization. LCST is a function of the polymer, solvent and crosslink composition, additives, and concentration of the responsive gel. It is desirable to effect such a transition at as low a temperature as possible because of the high amount of energy required in the
15 heating step. HPC, with an LCST of 42°C, is a particularly desirable responsive gel.

A "bead" is used herein to mean a small, substantially spherical object. The beads of the present invention may have a diameter in the collapsed state of no more than 600 μ m, and preferably having a mean
20 diameter to median diameter ratio of less than 1.2.

A "gel", as used herein, is a material between the solid and liquid state, in which a pure or mixed solvent or solution is entrained within a crosslinked polymer network. By "pure or mixed solvent and/or solution", as stated herein, it is recognized that a mixture of solvents may be absorbed
25 by the polymer network. Additionally, the solvent may include salts or other additives so as to form a solution, which may also be absorbed or entrained within the polymer network.

A "responsive gel", as used herein, is a gel which will undergo reversible swelling (entraining solvent) and collapsing (releasing solvent)
30 upon exposure to an external environmental condition, such as, for example,

temperature, pH, solvent concentration, electric field, photon irradiation, solution ionic strength and pressure. Additionally, the gel may be responsive to any of the above environmental stimuli which is triggered by application of an independent environmental condition. For example, 5 chromophores may be activated to change the pH or photon irradiation may generate heat. In order to be classified as a "responsive" gel, the gel must respond to a very small change in environmental conditions. A volumetric change of at least 20 percent in response to the small change in environmental stimulus is typical, in which the gel expands from a less 10 liquid-filled state (collapsed state) or a dry state to a more liquid-filled state (expanded state). When that solvent is water, or substantially water, the gel is known as a "responsive hydrogel".

Another aspect of the invention is a responsive cellulose gel bead having a diameter in a collapsed state of less than 600 μm , the collapsed 15 state at a temperature of no greater than 75°C. The responsive gel bead may be capable of responsively absorbing at least 5 gram solvent per milliliter of collapsed gel, as determined from a collapsed state at a temperature of no more than 75°C. This ratio is known as the "swelling ratio". The responsive gel bead may additionally be capable of responsively 20 absorbing at least 5 gram solvent per milliliter of collapsed gel in less than one hour or of absorbing and releasing at least 5 gram solvent per milliliter of collapsed gel in less than two hours, as determined from a collapsed state at a temperature of no more than 75°C. The "collapsed state" is that condition of the responsive gel in which substantially all unbound solvent is 25 released from the gel with the concomitant volume reduction. Some amount of bound solvent remains within the gel, which may be as high as 60% wt/wt of the collapsed gel. The collapsed state is determined under operating conditions which are optimal condition for a particular application. For example, in the situation where a temperature increase causes the 30 collapse of the responsive gel, a temperature is selected to be as high above

the LCST as is practical for the intended application of the gel. A typical collapsed state is no more than 20°C above the LCST of the responsive gel (eg, 75°C for a gel with an LCST of 55°C). For the responsive gel beads of the present invention having an LCST of no more than 55°C, the
5 collapsed state occurs at no more than 75°C.

Similar limitations may exist for other environmental conditions which trigger the gel response, i.e., pH, etc. A "collapsed state" is distinguished from "dry state" in which considerable time and energy is expended to remove substantially all solvent, including bound solvent, from the gel.

10 In a typical suspension crosslinking process, an aqueous polymer suspension is introduced into a continuous organic phase. The polymer suspension must be immiscible in the continuous organic phase. When the polymer is present in the aqueous phase and introduced into a continuous organic phase, as is the case for the cellulose ether polymers of the present
15 invention, the process is known as "inverse suspension crosslinking". The aqueous phase containing the polymer is agitated or stirred in the continuous organic phase, thereby dispersing the aqueous phase as droplets in the continuous organic phase. A crosslinker is included in the suspension which crosslinks the polymer. The crosslinker is preferably a bi-functional or
20 multi-functional chemical compound which is capable of reaction with the polymer in the droplet across two or more sites on the polymer chains, thus forming a polymer network which retains the droplet size and shape. The crosslinker is typically added to the aqueous suspension prior to dispersion into the organic phase, although it may be added during or after dispersion
25 of the aqueous phase into the continuous organic phase. In addition, surfactant and/or compatibilizing agents may be added to the continuous organic phase to stabilize droplet formation and control droplet size. Defoaming agents may be added to the aqueous solution to promote droplet formation and avoid foaming.

Flodin *et al.* teach a method of making EHEC gel beads by dispersing an aqueous colloidal suspension of the cellulose ether polymer and a high amount of epichlorohydrin crosslinker into an aromatic hydrocarbon or halogenated hydrocarbon solvent. EHEC has been determined to be a responsive polymer and the beads manufactured by Flodin *et al.* should be expected to be responsive although not usefully so within the objects of this invention. Attempts to prepare responsive HPC gel beads according to the method of Flodin *et al.* were reported to be unsuccessful (Stevin Gehrke, private communication) and were also unsuccessful in our laboratories. In particular, the crosslinker disclosed by Flodin *et al.* (epichlorohydrin) does not produce responsive HPC gel beads. Further, an HPC-precipitate apparently is formed during the suspension crosslinking of HPC in toluene. This has been observed by the applicants when the following procedure is carried out.

15 An HPC suspension was prepared as for a suspension crosslinking reaction, that is, an aqueous colloidal suspension containing 10-22% wt/wt HPC in water was hydrated by standing for a period of at least eight hours. Approximately one part of the hydrated HPC polymer suspension is placed into a vessel containing five parts toluene (an aqueous to organic ratio of approximately 17%). One sample remains at room temperature and the other is cooled to approximately 10°C overnight. Observation of the samples after standing overnight revealed that both toluene solutions had developed a cloudy precipitate.

25 Applicants have discovered, however, that careful control of reaction conditions will result in the successful suspension crosslinking of HPC in toluene. In addition, applicants have identified a class of organic solvents which are technically and environmentally advantageous in the inverse suspension crosslinking process of the present invention. Further, applicants have determined reaction conditions which provide responsive gel beads from a range of starting polymers and which have a range of desirable

30

properties. Lastly, responsive gel beads advantageously may be prepared using lower levels of crosslinker as compared to Flodin *et al.*

A. Suitable precursors

- 5 Responsive gels may be made from any polymer which forms a responsive polymer network upon crosslinking. The polymer may be used individually or may be blended with other polymers. Additionally, the polymer may be an interpenetrating polymer network, in which at least one polymer interpenetrates the polymer network of another polymer.
- 10 Generally, the polymer may be a polysaccharide (including cellulose, starch, sugars, chitin and hyaluronic acid), polypeptides, and synthetic polymers, such as PVA and PEO.

Preferably, the responsive gel beads are prepared from a crosslinkable cellulose ether polymer that has an LCST of no more than 55°C. Preferred

15 polymers exhibit a low LCST in aqueous solutions. In preferred embodiments, the responsive cellulosic gel bead includes hydroxypropyl cellulose (HPC) and methyl cellulose (MC), and mixtures thereof, optionally blended with hydroxyethyl cellulose (HEC), carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC), ethylhydroxyethyl

20 cellulose (EHEC), hydroxymethyl cellulose (HMC), and methylhydroxyethyl cellulose (MHEC) and mixtures thereof. A most preferred cellulose ether is HPC because of its low LCST of 42-46°C. Blends of cellulose ethers result in responsive gels with properties imparted by all cellulose ethers used.

25 IPNs of a cellulose ether with another, non-cellulose ether polymer can result in a responsive gel with properties typical of the cellulose ether component.

B. Crosslinking Agents

The additional requirement for the practice of this invention is that the

30 gel be crosslinkable, preferably chemically crosslinkable. Any reagent

which can react with two or more groups on the polymer can function as a crosslinker and convert that polymer to a gel. Polymers with reactive side groups such as a hydroxyl will be among the easiest to crosslink (note that these groups are also water soluble groups). It is thus most convenient if the crosslinker is water soluble.

Crosslinkers suitable for polymers include acetaldehyde, formaldehyde, glutaraldehyde, diglycidyl ether, vinyl sulfone (also known as divinyl sulfone; DVS), diisocyanates, epichlorohydrin, dimethylol urea, phosphoryl chloride, trimetaphosphate, trimethylomelamine, polyacrolein, and ceric ion redox systems. Crosslinkers suitable, in particular, for cellulose ethers include glutaraldehyde, vinyl sulfone and dimethylol urea. Vinyl sulfone is a preferred crosslinker for cellulose ethers. The crosslinker level is generally about 3 to about 100 microliter per gram dry polymer and preferably about 8.5 to about 40 microliter per gram dry polymer. The crosslinking agent effects partial crosslinking of the polymer by changing the crosslinking density, and provides a means of controlling the gel's mechanical strength, swelling degree, and intensity of the volume change trigger.

20 C. Continuous organic phase

A solvent which does not cause a precipitate is preferred for a number of reasons, including ability to view the ingredients during reaction and increased ease of workup of the synthesized beads. In addition, it is preferred to use a solvent in which the crosslinker is not soluble, since the crosslinker is quite expensive and is not easily disposed of. Additionally, any of the crosslinker which dissolves in the solvent may be lost to the reaction and may deleteriously affect the properties of the gel beads. It is preferred to minimize the quantity of crosslink used to insure there is no excess.

Solvents which are most preferred include high molecular weight aliphatic hydrocarbons, such as octane, nonane, decane, undecane, dodecane and, in particular, straight chain paraffinic or petroleum-based hydrocarbons, and mixtures and blends thereof. The class of solvents identified as "fine mineral oils" are preferred. Fine mineral oils typically are high purity hydrocarbon mixtures having a high boiling point (above 150°C) and relatively low viscosity (ca. 2 cSt at room temperature). Commercially available solvents meeting the above description includes Witsol 45-71B (petroleum-based hydrocarbon; Hercules), Norpar-12 (paraffinic hydrocarbon of various chain length; Exxon) and Isopar-L (iso-paraffinic hydrocarbon of various chain length; Exxon). The crosslinker is less soluble in such non-polar saturated hydrocarbons than in aromatic hydrocarbons or even shorter chained aliphatic hydrocarbons. The reduced solubility of the crosslinker in the continuous organic phase results in reduced loss of the crosslinker into the secondary phase and better control of the crosslinking process. Successful suspension crosslinking reactions have been carried out in Witsol 45-71B, Norpar-12, Isopar-L and high purity paraffins. The success of fine mineral oils as the organic solvent is surprising since one would not expect that a solvent of viscosity greater than low M_w hydrocarbons advantageously could be used in a inverse suspension crosslinking reaction due to the negative effects of solution viscosity on bead quality.

Solvents which are acceptable, but not preferred, include hexane, heptane, cycloalkanes such as cyclohexane and decalin, benzene, toluene, xylenes, ethylbenzenes and mesitylenes. Successful suspension crosslinking reactions have been carried out in toluene and decalin.

Many of the solvents which are preferred according to the above criteria are also preferred for environmental and manufacturing safety reasons. Of particular concern is the selection of a solvent of low toxicity

and having a low flash point. These environmental and manufacturing safety factors should be kept in mind when selecting the solvent.

D. Additives

5 Additives may be included in both the aqueous polymer phase and the continuous organic phase to promote and stabilize the formation of the suspended polymer droplets. To this end, surfactant and/or compatibilizing agents may be added to the continuous organic phase. Surfactants include, by way of example and in no way limited to, Span's, including Span-80
10 (Lonza), Tween's, including Tween-80, -81, -65, -60, and -85 (Lonza), Glycosperse 0-5 (Lonza, CAS No. 9005-65-6), Glycosperse TS-20 (Lonza), Arlacel-83 (Lonza, CAS No. 8007-43-0), Arlacel-186 (Lonza), G946 (ICI), Glycomul S (Lonza), Glycomul L (Lonza), Igepal's, including Igepal 520, 530 (Rhone-Poulenc), Atsurf 594 (ICI), Hypermer 2296 (ICI), Hypermer
15 (B246), Surfynol CT-111 (Air Products) and Surfynol 420 (Air Products). Further, defoamers may be added to the aqueous polymer phase to suppress foaming of the suspension and encourage formation of the suspended polymer droplets. Defoamers include, by way of example and in no way limited to, Surfynol CT-111 (Air Products), Surfynol 420 (Air Products),
20 Surfynol TG (Air Products), L371 (Drew), L474 (Drew), L475 (Drew), Y250 (Drew), L418 (Drew), and L139 (Drew).

Alternatively and/or additionally, a compatibilizing agent may be added to the two-phase system, either into the organic solvent or into the aqueous polymer suspension. A compatibilizing agent, as that term is used
25 herein, means a polymer, oligomer or compound that is substantially non-reactive to the components of the crosslinking system and which includes both hydrophilic and hydrophobic regions. A compatibilizing agent may be a copolymer of hydrophobic and hydrophilic components. In particular, the compatibilizing agent may be a copolymer of vinylpyrrolidinone and long
30 chain α -olefins or it may be an alkylated poly(vinylpyrrolidinone). Suitable

compatibilizing agents include, by way of example and in no way limited to, poly(vinyl-pyrrolidinone/1-hexadecene) copolymer and poly(vinylpyrrolidinone/1-eicosene) copolymer. The compatibilizing agent acts in a manner similar to a surfactant, in that it contains hydrophilic regions which interact favorably with the aqueous soluble solution and hydrophobic regions which interact favorably with the organic solvent. It is not expected to have the traditional hydrophobic head and hydrophilic tail arrangement of a surfactant.

Additionally, antimicrobial agents, antifungal agents and preservatives may be added to the responsive gel to improve the shelf-life of the gel. Adhesive modifiers, which reduce or increase the stickiness of the gel beads, may also be included in the gel bead or on the surface. Further, other surface modifiers or coatings may be applied to the bead to improve surface hardness, control surface adsorption, control pore size, or modify other characteristics of the surface of the bead. Exemplary antimicrobial agents, antifungal agents and surface modifiers include, by way of example only, Dowicil®, butylated hydroxytoluene, methionine, cysteine, ascorbic acid, catalase, superdioxide dismutase, glutathione, parabens, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate, polyethyleneglycol and polyethyleneoxide.

E. Bead Size Determination

To measure beads in an "as synthesized" state, a random sample of beads is removed from the reaction vessel prior to neutralizing and wash cycling and placed into a petri dish. A subset of at least twenty beads (and in some cases fifty or more) are separated indiscriminately and measured with a Hand Wetzler microscope (Seiler W0042) equipped with a Hitachi color camera (KP-C550, CCD) and Optech (Imagen HR 1024), Video Measuring System. After several repetitions of measuring 100 beads and randomly selecting subsets of twenty beads, it was determined that twenty

beads provided a reasonable representation of the batch. For experiments in which exceptionally small beads were produced the average calculation of the subset of twenty was comprised of only those beads which measured larger than 30 μm in diameter, those less than 30 μm were omitted from the calculation.

To measure the beads in a collapsed state, a random sample of beads which have been neutralized and washed as described in the Protocol, hereinbelow, are collapsed overnight in a constant temperature bath of 65°C. Approximately twenty of these beads are introduced into a flow cell with a constant temperature circulating bath which permits the beads to be maintained at constant temperature during measurement. After equilibration, the beads are measured with a Hand Wetzler microscope (Seiler W0042) equipped with a Hitachi color camera (KP-C550, CCD) and Optech (Imagen HR 1024), Video Imaging System, as above.

A variety of reaction variables affect the final gel bead diameter for a given polymer and crosslinking density, for example, aqueous suspension viscosity (which is a function of the polymer molecular weight and concentration), organic solvent viscosity, degree of agitation of the two-phase system, and use and type of surfactant and/or compatibilizing agents and defoamers (preferential surface tension). In general, the need to use high M_w polymers at high concentrations in order to obtain a gel with a high swelling ratio must be balanced with the need to reduce solution viscosity to promote the breakup of the suspension into small droplets. The polymer concentrations and crosslinker concentrations found in the Examples, hereinbelow, are exemplary ranges which balance these conflicting needs. Surfactant and/or compatibilizing agents are particularly useful in this regard.

F. Measuring Swelling Behavior (Swelling Ratio)

The amount of solvent absorbed from the collapsed state over a given temperature range is determined as follows. A quantity of gel beads is placed in a graduated cylinder at room temperature and solvent is added. The graduated cylinder is held in a water bath at the stated elevated
5 temperature (above the LCST) for the time indicated. The height of the collapsed gel is determined from the volume indications of the graduated cylinder. The graduated cylinder containing the gel beads is then held in a water bath at a temperature below the LCST (typically, room temperature) for the time indicated and the volume of the expanded gel beads is then
10 measured from the graduated cylinder. The amount of solvent absorption is the difference in heights (assuming void volume remains constant) and the swelling ratio is the ratio of the volume of solvent absorbed to the volume of the collapsed gel beads.

15 **G. Measuring Swelling Kinetics (Swelling Rate)**

The amount of solvent absorbed from the collapsed state over a given temperature range and in a given period of time is determined as follows. A quantity of gel beads is placed in a graduated cylinder at room temperature and solvent is added. The graduated cylinder is held in a water bath at the
20 stated elevated temperature (above the LCST) and agitated for the time indicated. The height of the collapsed gel is determined from the volume indications of the graduated cylinder. The graduated cylinder containing the gel beads is then held in a water bath at a temperature below the LCST (typically, room temperature) and agitated for the time indicated and the
25 volume of the expanded gel beads is then measured from the graduated cylinder. The rate of solvent absorption is the swelling rate and is determined as the ratio of the volume of solvent absorbed to the volume of the collapsed gel beads per unit time.

The invention may be understood with reference to the following examples which are presented for the purposes of illustration only and which are not intended to be in any way limiting of the scope of the invention.

5

Examples

The effect of pH, crosslinker and polymer levels and ratio of aqueous to organic phase were evaluated to determine effective operating conditions for responsive gel bead formation. The general procedure for design of the inverse suspension crosslinking reactions of responsive gel beads is as follows.

General Protocol. A polymer colloidal suspension (100 mL) containing 10-32% wt/wt cellulose ether polymer and deionized water (Millipore, Alpha-Q) is hydrated over night. To this suspension is added 2.0 mL of 5 N NaOH (Baker, Catalogue No. JT37722-11) such that the pH of the solution is ca. 12.5 and the solution is allowed to stand for approximately 45 minutes. NaOH may optionally be added when the polymer suspension originally is prepared.

A 500 mL baffled flask with a three neck top (Chemglass CG-1951 and CG-1960) is used for the reaction vessel. The impeller used is a six flat-bladed turbine (Lightnin R100 2.0") with a 5/16" stainless steel shaft which is placed in the center neck of the reaction vessel. An organic solvent is used for the continuous organic phase. The organic solvent (ca. 350-450 mL) is introduced into the 500 mL baffled flask equipped with the impeller blade. The organic solvent is stirred at a constant rate in the range of 300-1000 rpm (Lab Assistants RZR-2000). Immediately before introduction of the cellulosic polymer suspension into the stirred organic solvent, a crosslinker (in the range of 3.0-100 microliters per gram dry polymer) is added to the polymer suspension and mixed for approximately 30 seconds. The polymer/crosslinker suspension is added to the stirred organic solvent. The aqueous component is approximately 13-20% vol/vol of a total volume

of 500 mL reaction mixture. Beads are observed almost immediately and the reaction vessel is allowed to stir overnight at room temperature to complete the crosslink reaction.

The typical method for neutralizing and washing the beads is to
5 decant the continuous phase solvent from the beads and place the beads into a clean beaker. An acidic solution (pH 3.0-4.0) is made by dissolving approximately one gram of ammonium chloride (Fisher, Catalog No. A661-500) in 100 mL of deionized water (Millipore, Alpha-Q) and adding two drops of concentrated hydrochloric acid (Aldrich, Catalog No. 25,814-8) to
10 the solution. The acidic solution is added to the beads while simultaneously monitoring the pH of the bead/acid solution with a pH meter (Orion, 420A, with Orion triode electrode) to a pH of 7.0-7.5. The beads in solution are then heated in this neutralizing solution at 50-60°C to collapse the beads. The water is filtered off, 100-150 mL of fresh deionized water (Millipore,
15 Alpha-Q) is added and the beads are allowed to swell to complete the thermal cycle. This thermal cycling is done for a total of three times.

Example 1: Effect of crosslinker concentration and polymer concentration on bead manufacture. A range of polymer and crosslinker levels were evaluated for their effect on bead formation and swelling
20 capacity. HPC polymer suspensions containing various amounts of crosslinker and HPC polymer were dispersed into Norpar-12 (Exxon). The aqueous to organic volume ratio was held constant at 17% aqueous (85 mL aqueous suspension and 415 mL Norpar-12). In those cases where beads were formed, the swelling ratio was determined by measuring the
25 equilibrium volume change over a temperature range of 25°C (selected between the temperature range of 30°C to 65°C). Experimental results indicated that there is a strong synergistic effect of polymer concentration and crosslinker concentration, as illustrated in Table 1.

Table 1. Formation of HPC Beads.^a

Exper. #	XL ^b	wt% HPC polymer ^c	swelling ratio
1-1	3.0	7.5	no beads
1-2	3.0	12.5	6.9
1-3	5.0	7.5	no beads
1-4	5.0	12.5	3.2
1-5	2.6	10.0	no beads
1-6	5.4	10.0	4.3
1-7	4.0	6.5	no beads
1-8	4.0	13.5	3.7
1-9	1.7	15.0	4.7
1-10	0.85	20.0	4.7
1-11	0.85	15.0	no beads
1-12	1.7	20.0	2.7
1-13	2.0	17.5	3.4
1-14	1.28	13.2	no beads
1-15	1.28	17.5	4.3
1-16	1.28	21.8	3.4
1-17	0.54	17.5	no beads
1-18	1.28	17.5	4.3

^a Norpar-12 = organic solvent; ^b microliter crosslinker ($\times 10^{-1}$) per gram dry cellulose polymer; ^c wt% in a total 100 g suspension.

Beads can not be made from an inverse polymer crosslinking process if the crosslinker level is too low or if the polymer concentration in water is too low. At high polymer concentration, use of a lower crosslinker level is possible. For example, no beads were formed with a crosslinker level of 5.0 microliter per gram dry polymer when the polymer concentration was 7.5% wt/wt; or at a crosslinker level of 26 microliter per gram dry polymer

when the polymer concentration was 10% wt/wt. However, satisfactory beads were formed from an inverse suspension crosslinking process with a crosslinker level of 8.5 microliter per gram dry polymer and a polymer concentration of 20% wt/wt. This is desirable from a commercial standpoint because the crosslinker is the most expensive component of the gel and because lower crosslinker levels result in gel beads of higher swelling ratios.

A responsive surface plot illustrating bead formation under a range of crosslinker and polymer levels is shown in the Figure. A value of "1" is assigned to conditions producing beads and a value of "0" is assigned to conditions which did not produce beads. The regression analysis used resulted in a continuous function, which can be viewed as the likelihood of bead formation under the stated conditions.

The data suggests that a useful region for responsive gel bead synthesis can be defined. The line ranging through the point at a crosslinker level of 21-28 microliter per gram dry polymer and a polymer concentration of 10% wt/wt to the point defined by a crosslinker level of 5.0 to 8.0 microliter per gram dry polymer and a polymer concentration of 20% wt/wt defines an area where responsive gel beads will be formed. The range of acceptable reaction conditions is limited by an upper boundary, where the polymer solution becomes so viscous that it is unmanageable and unpourable. Under the present conditions, this occurs at a polymer concentration for HPC (M_w 95k) of about 22-25% wt/wt.

In conclusion, the responsive surface of the Figure indicates that, where the reactions conditions satisfy the following equation,

$$[\text{polymer}] + 5 \times [\text{crosslinker} \times 10^{-1}] > 24,$$

satisfactory responsive gel beads may be prepared. More desirably, the responsive surface of the Figure indicates that, where the reactions conditions satisfy the following equation

$$[\text{polymer}] + 6.25 \times [\text{crosslinker} \times 10^{-1}] > 23.125,$$

satisfactory responsive gel beads may be prepared.

Example 2: Inverse Suspension Crosslinking of Hydroxypropyl

Cellulose (M_w 95k) with Vinyl Sulfone using Glycosperse 0-5 Surfactant.

Twenty grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 80 mL of deionized water and allowed to hydrate overnight. To this suspension
5 was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes. The continuous phase solvent, Norpar-12 (415 mL, paraffinic hydrocarbon, Exxon) was added to a 500 mL baffled reaction vessel equipped with an
10 impeller blade, and stirring was initiated at 450 rpm. To the agitated solvent was added 100 μ l of Glycosperse 0-5 (Lonza, CAS No. 9005-65-6) and the surfactant was dispersed for 15 minutes.

To the hydrated polymer suspension was added 170 μ l of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30
15 seconds. This polymer suspension was then poured into the reaction vessel which was being agitated in the presence of the surfactant. The mixture was allowed to react at room temperature overnight. The beads were worked up in the typical manner as described in the Protocol.

In a collapsed state (65°C 20°C above the LCST) the average
20 diameter of the beads was 478 μ m with a median diameter of 439 μ m (a mean to median ratio of 1.09). In the as synthesized state, the average diameter was 635 μ m with a standard deviation of 148 μ m. These beads have a swelling ratio of 6.8 after a cycle of swelling at 30°C and subsequent collapse at 55°C in two hours (1 hr at 30°C and 1 hr at 55°C). At near
25 equilibrium (>24 hours at constant temperature before measurement), the total swell ratio from room temperature to 65°C was 11.6. A swell ratio of 3.2 was achieved after 30 minutes thermal cycle between 30°C and 55°C (15 minutes at 55°C and 15 minutes at 30°C). When thermally cycled for two hours in a 1% dextran blue/deionized water solution between 30°C and
30 55°C (1 hr at 55°C and 1 hr at 30°C), the swelling ratio was 5.5.

Example 3: Inverse Suspension Crosslinking of Hydroxypropyl

Cellulose (M_w 95k) with Vinyl Sulfone using Arlacel-83 Surfactant.

Twenty grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 80 mL of deionized water and allowed to hydrate overnight. To this suspension was
5 added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes. The continuous phase solvent, Norpar-12 (415 mL, paraffinic hydrocarbon, Exxon) was added to a 500 mL baffled reaction vessel equipped with an impeller blade,
10 and stirring was initiated at 450 rpm. To the agitated solvent was added 100 μ L of Arlacel-83 (Lonza, CAS No. 8007-43-0) and the surfactant was dispersed for 15 minutes.

To the hydrated polymer suspension was added 170 μ L of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30
15 seconds. This polymer suspension was then poured into the reaction vessel which was being agitated in the presence of the surfactant. The mixture was allowed to react at room temperature overnight. The beads were worked up in the typical manner as described in the Protocol.

In a collapsed state (20°C above the LCST) the average diameter of
20 the beads was 454 μ m with a median diameter of 444 μ m (a mean to median ratio of 1.02) and a standard deviation of 80 μ m. In the as synthesized state, the average diameter was 698 μ m with a standard deviation of 217 μ m. At near equilibrium (>24 hrs at constant temperature before measurement), the total swell ratio from 30°C to 65°C was 4.1.

25 Example 4: Inverse Suspension Crosslinking of Hydroxypropyl

Cellulose (M_w 95k) with Vinyl Sulfone in Witsol 45-71B.

Twenty grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 80 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5.

The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes.

The continuous phase solvent, Witsol 45-71B (415 mL, petroleum hydrocarbon, Hercules) was added to a 500 mL baffled reaction vessel
5 equipped with an impeller blade, and stirring was initiated at 450 rpm. To the hydrated polymer suspension was added 170 μ L of vinyl sulfone (Sigma, Catalog No. V9501), which was then stirred with a glass rod for 30 seconds. This polymer suspension was then poured into the agitating reaction vessel. The mixture was allowed to react at room temperature
10 overnight.

The beads were worked up in the typical manner as described in the Protocol. The average diameter of the collapsed bead was 1.75 mm with a standard deviation of 0.243 mm. The median diameter of the beads was 1.69 mm (a mean to median ratio of 1.04). The significantly larger bead
15 size reflects the absence of surfactant in the process.

Example 5: Inverse Suspension Crosslinking of Hydroxypropyl Cellulose (M_w 95k) with Vinyl Sulfone in Isopar-L. Twelve and one-half (12 1/2) grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 80 mL of deionized water and allowed to hydrate overnight. To this suspension
20 was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes. The continuous phase solvent, Isopar-L (415 mL, iso-paraffinic hydrocarbon, Exxon) was added to a 500 mL baffled reaction vessel equipped with an
25 impeller blade, and stirring was initiated at 450 rpm. To the hydrated polymer suspension was added 375 μ L of vinyl sulfone (Sigma, Catalog No. V9501), which was then stirred with a glass rod for 30 seconds. This polymer suspension was then poured into the agitating reaction vessel. The mixture was allowed to react at room temperature overnight.

The beads were worked up in the typical manner as described in the Protocol. The equilibrium swell ratio from 30°C to 55°C was 5.0.

Example 6: Inverse Suspension Crosslinking of Hydroxypropyl Cellulose (M_w 95k) with Vinyl Sulfone in Toluene.

5 Ten grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 90 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes.

10 The continuous phase solvent, toluene, (415 mL, Fisher, A.C.S. Grade) was added to a 500 mL baffled reaction vessel equipped with an impeller blade, and stirring was initiated at 450 rpm. To the hydrated polymer suspension was added 260 μ L of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30 seconds. This polymer
15 suspension was then poured into the agitating reaction vessel. The mixture was allowed to react at room temperature overnight.

The beads were worked up in the typical manner as described in the Protocol.

Example 7: Inverse Suspension Crosslinking of Methyl Cellulose

20 with Vinyl Sulfone in Norpar-12. Twelve grams of MC (Dow, Methocel A15LV) was added to 88 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for
25 45 minutes.

The continuous phase solvent, Norpar-12 (415 mL, paraffinic hydrocarbon, Exxon), was added to a baffled reaction vessel equipped with an impeller blade, and stirring was initiated at 450 rpm. To the hydrated polymer suspension was added 600 μ L of vinyl sulfone (Sigma, Catalog No.
30 V9501) and then stirred with a glass rod for 30 seconds. This polymer

suspension was then poured into the agitating reaction vessel. The mixture was allowed to react at room temperature overnight.

The beads were worked up in the typical manner as described in the Protocol. The near equilibrium swell ratio measured from room temperature
5 to 65°C was 0.5.

Example 8: Inverse Suspension Crosslinking of Hydroxypropyl Cellulose with Vinyl Sulfone using Surfynol CT-111 Defoamer. Twenty grams of HPC (Aqualon, Klucel LF NF, M_w 95k) and 500 μ l of Surfynol CT-111 (Air Products) was added to 80 mL of deionized water and allowed
10 to hydrate overnight. To this suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes.

The continuous phase solvent, Norpar-12 (415 mL, paraffinic
15 hydrocarbon, Exxon), was added to a baffled reaction vessel equipped with an impeller blade, and stirring was initiated at 450 rpm. To the hydrated polymer suspension was added 170 μ l of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30 seconds. This polymer suspension was then poured into the agitating reaction vessel. The mixture
20 was allowed to react at room temperature overnight.

The beads were worked up in the typical manner as described in the Protocol. In the collapsed state (20°C above the LCST), the average diameter of the beads was 841 μ m and the median diameter was 819 μ m (a mean to median ratio of 1.03). The equilibrium swell ratio measured from
25 30°C to 55°C was 7.4. The larger bead size was due to the absence of surfactant in the process.

Example 9: Inverse Suspension Crosslinking of Hydroxypropyl Cellulose (M_w 140k) with Vinyl Sulfone in Norpar-12. Seventeen and one-half (17 1/2) grams of HPC (Aqualon, Klucel JF, M_w 140k) was added to
30 82.5 mL of deionized water and allowed to hydrate overnight. To this

suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes.

The continuous phase solvent, Norpar-12 (415 mL, paraffinic hydrocarbon, Exxon), was added to a baffled reaction vessel equipped with an impeller blade, and stirring was initiated at 450 rpm. To the hydrated polymer suspension was added 223 μ l of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30 seconds. This polymer suspension was then poured into the agitating reaction vessel. The mixture was allowed to react at room temperature overnight.

The beads were worked up in the typical manner as described in the Protocol. The near equilibrium swelling ratio was 6.0 from room temperature to 65°C.

Example 10: Inverse Suspension Crosslinking of Hydroxypropyl Cellulose (M_w 95k) with Vinyl Sulfone in the Continuous Phase. Twenty grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 80 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes.

The continuous phase solvent, Norpar-12 (415 mL, paraffinic hydrocarbon, Exxon) was added to a 500 mL baffled reaction vessel equipped with an impeller blade, and stirring was initiated at 450 rpm. The polymer suspension was poured into the agitating reaction vessel and allowed to mix for several minutes. To the organic solvent was added 340 μ l of vinyl sulfone (Sigma, Catalog No. V9501). The mixture was allowed to react at room temperature overnight.

The beads were worked up in the typical manner as described in the Protocol. The near equilibrium swelling ratio was 2.3 from 30°C to 55°C.

Example 11: Inverse Suspension Crosslinking of Hydroxypropyl Cellulose (M_w 95k) with Vinyl Sulfone at 1000 rpm. Ten grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 90 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 drops of
5 a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes.

The continuous phase solvent, Norpar-12 (415 mL, paraffinic hydrocarbon, Exxon) was added to a baffled reaction vessel equipped with
10 an impeller blade, and stirring was initiated at 1000 rpm (Caframo RZRI stirrer, rpm confirmed with Onosoki Tachometer HT-3100). To the hydrated polymer suspension was added 400 μ L of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30 seconds. This polymer suspension was then poured into the reaction vessel which was
15 being agitated. The mixture was allowed to react at room temperature overnight.

The beads were worked up in the typical manner as described in the Protocol. The near equilibrium swelling ratio from 30°C to 55°C was 7.0.

Example 12: Inverse Suspension Crosslinking of Hydroxypropyl Cellulose (M_w 95k) with Vinyl Sulfone using Ganex V216 Compatibilizing Agent. Twenty grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was
20 added to 80 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly
25 to disperse the basic solution, and was then allowed to stand for 45 minutes. The continuous phase solvent, Norpar-12 (352.5 mL, paraffinic hydrocarbon, Exxon) was added to a 500 mL baffled reaction vessel equipped with an impeller blade, and stirring was initiated at 450 rpm. To the agitated solvent was added 62.5 mL of a 2.5% vol/vol solution of Ganex

V216 (poly(vinylpyrrolidinone/1-hexadecene), ISP Technologies, Inc.) in Norpar-12 and the solution was dispersed for 30 minutes.

To the hydrated polymer suspension was added 170 μ l of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30
5 seconds. This polymer suspension was then poured into the reaction vessel which was being agitated in the presence of the compatibilizing agent. The mixture was allowed to react at room temperature overnight. The beads were worked up in the typical manner as described in the Protocol.

In the "as synthesized" state (beads sampled directly from the reaction
10 vessel at a temperature of not more than 30°C), the average diameter is 84 μ m with a standard deviation of 42 μ m. The beads have a swell ratio of 7.5 as determined over two hours from 32.5°C to 62.5°C. The beads also have a swell ratio of 7.1 as determined over 30 minutes from 35°C to 60°C.

Example 13. Inverse Suspension Crosslinking of Hydroxypropyl
15 Cellulose (M_w 95k) with Vinyl Sulfone using Ganex V216 Compatibilizing Agent on a Five Liter Scale. Two hundred grams of HPC (Aqualon, Klucel LF NF, M_w 95k) was added to 800 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 mL of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was
20 stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes. The continuous phase solvent, Norpar-12 (3525 mL, paraffinic hydrocarbon, Exxon) was added to a 5000 mL baffled reaction vessel equipped with an impeller blade (Lightnin R100 4.0; 5/8" shaft), and stirring was initiated at 300 rpm (lightnin Labmaster). To the agitated
25 solvent was added 625 mL of a 2.5% vol/vol solution of Ganex V216 (poly(vinylpyrrolidinone/1-hexadecene)), ISP Technologies, Inc.) in Norpar-12 and the solution was dispersed for 30 minutes.

To the hydrated polymer suspension was added 1.7 mL of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30
30 seconds. This polymer suspension was then poured into the reaction vessel

which was being agitated in the presence of the compatibilizing agent. The mixture was allowed to react at room temperature overnight. The beads were worked up in the typical manner as described in the Protocol.

In the as synthesized state, meaning beads samples directly from the reaction vessel at a temperature of less than 30°C, the average diameter is 136 μm with a standard deviation of 77 μm . The beads have a swell ratio of 6.7 as determined over two hours from 32.5°C to 62.5°C. The beads also have a swell ratio of 7.2 as determined over 30 minutes from 35°C to 60°C.

Example 14: Inverse Suspension Crosslinking of

Hydroxypropylmethyl Cellulose with Vinyl Sulfone using Ganex V216
Compatibilizing Agent. Twenty seven grams of HPMC (Dow, Methocel 5LV) was added to 72.5 mL of deionized water and allowed to hydrate overnight. To this suspension was added 20 drops of a 5N NaOH solution to form a solution of approximately pH 12.5. The suspension was stirred thoroughly to disperse the basic solution, and was then allowed to stand for 45 minutes. The continuous phase solvent, Norpar-12 (352.5 mL, paraffinic hydrocarbon, Exxon) was added to a 500 mL baffled reaction vessel equipped with an impeller blade, and stirring was initiated at 450 rpm. To the agitated solvent was added 62.5 mL of a 2.5% vol/vol solution of Ganex V216 (poly(vinylpyrrolidinone/1-hexadecene), ISP Technologies, Inc.) in Norpar-12 and the solution was dispersed for 30 minutes.

To the hydrated polymer suspension was added 825 μl of vinyl sulfone (Sigma, Catalog No. V9501) and then stirred with a glass rod for 30 seconds. This polymer suspension was then poured into the reaction vessel which was being agitated in the presence of the compatibilizing agent. The mixture was allowed to react at room temperature overnight. The beads were worked up in the typical manner as described in the Protocol.

In the "as synthesized" state (beads sampled directly from the reaction vessel at a temperature of not more than 30°C), the average diameter is 377 μm with a standard deviation of 130 μm .

Applications

A number of applications for gel beads are listed in Gel Science, Inc. brochures "Gel Sciences, the leader in Engineered Response Gels", G001-2/94-10M; "Separations", S001-2/94-10M, and "Controlled Release",

5 CR001-2/94-10M, which are included herein by reference. These applications include:

- 1) Separations, or reduction in the solvent level, of a number of products including protein, food protein, other food components, minerals, oils, industrial waste, biological waste, human waste, chemicals and chemical
10 dispersions, and polymers and polymer dispersions;
- 2) Dewatering of mud, slurries, metal particulate slurries and dispersions, and molecular sieves;
- 3) Industrial applications, such as chromatography, cleaning chemicals, inks and coatings, adhesives, waxes fertilizer, organic vapor removal, valves and
15 oil spill cleanups;
- 4) Medical, pharmaceutical and diagnostic applications including electrophoresis, iontophoresis, free drug assay, spinal fluid diagnostics, assay, blood ultracentrifugation, cell culturing, wound dressing, exudate absorption and bacterial indicators; and
- 20 5) Toys.

Other embodiments of the invention will be apparent to those skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the
25 invention being indicated by the following claims.

What is claimed is:

1. A responsive gel bead, comprising:
a polymer which is chemically crosslinked with a bi-functional or multi-functional organic compound, the gel bead having an LCST of less than 55°C.
- 5 2. The responsive gel bead of claim 1, wherein the polymer is in a form selected from the group consisting of polymer blends and interpenetrating polymer networks.
3. The responsive gel bead of claim 1 having a diameter in a
10 collapsed state of less than 600 μm , the collapsed state at a temperature of no greater than 75°C.
4. The responsive gel bead of claim 1 or 3, characterized in that
15 the gel bead is capable of absorbing at least 5 grams solvent per milliliter of collapsed gel, wherein the collapsed gel is at a temperature of no greater than 75°C.
5. The responsive gel bead of claim 1 or 3, characterized in that
20 the gel bead is capable of responsively absorbing at least 5 gram solvent per milliliter of collapsed gel in one hour or less, wherein the collapsed gel is at a temperature of no greater than 75°C.
6. The responsive gel bead of claim 1 or 3, characterized in that
25 the gel bead is capable of responsively absorbing and releasing at least 5 gram solvent per milliliter of collapsed gel in two hours or less, wherein the collapsed gel is at a temperature of no greater than 75°C.
7. The responsive gel bead of claim 3, wherein the ratio of a mean diameter of the gel bead in a collapsed state to a median diameter of

the gel bead in a collapsed state is no more than 1.2, wherein the collapsed state is at a temperature of no greater than 75°C.

8. A responsive cellulosic gel bead, comprising:
 - 5 a cellulose ether polymer which is chemically crosslinked with a bi-functional or multi-functional organic compound, the cellulosic gel bead having an LCST of less than 55°C.
9. The responsive cellulosic gel bead of claim 8, wherein the
 - 10 cellulose ether polymer is in a form selected from the group consisting of polymer blends and interpenetrating polymer networks.
10. The responsive cellulosic gel bead of claim 8 having a diameter
 - 15 in a collapsed state of less than 600 μm , the collapsed state at a temperature no greater than 75°C.
11. The responsive cellulosic gel bead of claim 8 or 9,
 - characterized in that the gel bead is capable of absorbing at least 5 grams solvent per milliliter of collapsed gel, wherein the collapsed gel is at a - 20 temperature of no greater than 75°C.
12. The responsive cellulosic gel bead of claim 8 or 10,
 - characterized in that the gel bead is capable of responsively absorbing at least 5 gram solvent per milliliter of collapsed gel in one hour or less, - 25 wherein the collapsed gel is at a temperature no greater than 75°C.
13. The responsive cellulosic gel bead of claim 8 or 10,
 - characterized in that the gel bead is capable of responsively absorbing and releasing at least 5 gram solvent per milliliter of collapsed gel in two hours - 30 or less, wherein the collapsed gel is at a temperature no greater than 75°C.

14. The responsive cellulosic gel bead of claim 10, wherein the ratio of a mean diameter of the gel bead in a collapsed state to a median diameter of the gel bead in a collapsed state is no more than 1.2, wherein the collapsed gel is at a temperature no greater than 75°C.

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15. The responsive cellulosic gel bead of claim 8, 10 or 14, wherein the gel bead comprises a polymer selected from the group consisting of hydroxypropyl cellulose, methyl cellulose, and mixtures thereof.

10

16. The responsive cellulosic gel bead of claim 15, wherein the polymer is further blended with a polymer selected from the group consisting of hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose, ethylhydroxyethyl cellulose, hydroxymethyl cellulose, methylhydroxyethyl cellulose and mixtures thereof.

15

17. The responsive cellulosic gel bead of claim 11, wherein the gel bead comprises a polymer selected from the group consisting of hydroxypropyl cellulose, methyl cellulose, and mixtures thereof.

20

18. The responsive cellulosic gel bead of claim 17, wherein the polymer is further blended with a polymer selected from the group consisting of hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose, ethylhydroxyethyl cellulose, hydroxymethyl cellulose, methylhydroxyethyl cellulose and mixtures thereof.

25

19. The responsive cellulosic gel bead of claim 12, wherein the gel bead comprises a polymer selected from the group consisting of hydroxypropyl cellulose, methyl cellulose and mixtures thereof.

20. The responsive cellulosic gel bead of claim 19, wherein the polymer is further blended with a polymer selected from the group consisting of hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose, ethylhydroxyethyl cellulose, hydroxymethyl
5 cellulose, methylhydroxyethyl cellulose and mixtures thereof.

21. The responsive cellulosic gel bead of claim 13, wherein the gel bead comprises a polymer selected from the group consisting of hydroxypropyl cellulose, methyl cellulose and mixtures thereof.

10

22. The responsive cellulosic gel bead of claim 21, wherein the polymer is further blended with a polymer selected from the group consisting of hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose, ethylhydroxyethyl cellulose, hydroxymethyl
15 cellulose, methylhydroxyethyl cellulose and mixtures thereof.

23. The responsive cellulosic gel bead of claim 8, 9, 10 or 14, wherein the gel bead comprises hydroxypropyl cellulose.

20 24. The responsive cellulosic gel bead of claim 11, wherein the gel bead comprises hydroxypropyl cellulose.

25. The responsive cellulosic gel bead of claim 12, wherein the gel bead comprises hydroxypropyl cellulose.

25

26. The responsive cellulosic gel bead of claim 13, wherein the gel bead comprises hydroxypropyl cellulose.

27. A responsive gel bead, comprising:

a preformed polymer which is then chemically crosslinked with a bi-functional or multi-functional organic compound, the gel bead having a diameter of less than or equal to 400 μm as prepared and measured at a temperature of less than 30°C.

5

28. A responsive gel bead, comprising:

a preformed polymer which is then chemically crosslinked with a bi-functional or multi-functional organic compound, the gel bead having a diameter of less than or equal to 50 μm as prepared and measured at a temperature of less than 30°C.

10

29. A method for the manufacture of responsive cellulosic gel beads by inverse suspension crosslinking, comprising the steps of:

providing an aqueous suspension of a cellulose ether polymer, an organic solvent and a crosslinker, where the organic solvent is immiscible with the aqueous suspension;

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admixing the aqueous cellulose ether suspension, the organic solvent and the crosslinker to form a two-phase system, where the aqueous suspension and the organic solvent comprise the two phases of the system;

20

agitating the two-phase system sufficient to form droplets of the aqueous cellulose ether suspension in the organic solvent;

maintaining agitation of the two-phase system for a time sufficient to form crosslinked cellulose ether gel beads; and

recovering the crosslinked cellulose ether gel beads from the organic solvent.

25

30. The method of claim 29 wherein the crosslinker is selected from the group consisting of acetaldehyde, formaldehyde, glutaraldehyde, diglycidyl ether, vinyl sulfone (also known as divinyl sulfone; DVS), diisocyanates, epichlorohydrin, dimethylol urea, phosphoryl chloride,

30

trimetaphosphate, trimethylmelamine, polyacrolein, and ceric ion redox systems.

31. The method of claim 30, wherein the crosslinker is selected
5 from the group consisting of vinyl sulfone, glutaraldehyde and dimethylol urea.

32. The method of claim 29, 30 or 31, wherein the organic solvent
is a hydrocarbon selected from the group consisting of paraffinic
10 hydrocarbons, petroleum-based hydrocarbons, high purity mineral oils and mixtures thereof.

33. The method of claim 32, wherein the organic solvent is
selected from the group consisting of decane, octane, nonane, undecane,
15 dodecane, straight chain paraffinic and petroleum-based hydrocarbons and mixtures and blends thereof.

34. The method of claim 32, wherein the organic solvent comprises
a cycloalkane.
20

35. The method of claim 34, wherein the cycloalkane is selected
from the group consisting of cyclohexane and decalin.

36. The method of claim 32, wherein the organic solvent comprises
25 a fine mineral oil having a viscosity less than 2 cSt.

37. The method of claim 36, wherein the fine mineral oil is
selected from the group consisting of Norpar-12, Isopar-L, or Witsol 45-
71B.

38. The method of claim 29, 30 or 31, further comprising the step of admixing the crosslinker with the aqueous cellulose suspension prior to admixture with the organic solvent.

5 39. The method of claim 29, further comprising the step of admixing the organic solvent with the aqueous cellulose suspension prior to admixture with the crosslinker.

40. The method of claim 30, further comprising the step of
10 admixing the organic solvent with the aqueous cellulose suspension prior to admixture with the crosslinker.

41. The method of claim 32, further comprising the step of
admixing the organic solvent with the aqueous cellulose suspension prior to
15 admixture with the crosslinker.

42. The method of claim 33, further comprising the step of
admixing the organic solvent with the aqueous cellulose suspension prior to
admixture with the crosslinker.
20

43. The method of claim 34, further comprising the step of
admixing the organic solvent with the aqueous cellulose suspension prior to
admixture with the crosslinker.

25 44. The method of claim 35, further comprising the step of
admixing the organic solvent with the aqueous cellulose suspension prior to
admixture with the crosslinker.

45. The method of claim 36, further comprising the step of admixing the organic solvent with the aqueous cellulose suspension prior to admixture with the crosslinker.

5 47. The method of claim 29, 30 or 31, wherein the crosslinker is present at a level of about 3 to about 100 microliter per gram dry polymer.

48. The method of claim 29, 30 or 31, wherein the crosslinker is present at a level of about 7.5 to about 40 microliter per gram dry polymer.

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49. The method of claim 29, further comprising the step of admixing a surfactant into the organic solution.

50. The method of claim 32, further comprising the step of
15 admixing a surfactant into the organic solution.

51. The method of claim 29, further comprising the step of admixing a defoamer into the aqueous suspension.

20 52. The method of claim 29, further comprising the step of:
adding an additive selected from the group consisting of antimicrobial agents, antifungal agents, preservatives, adhesive modifiers, surface modifiers, carriers, compatibilizing agents and excipients.

25 53. The method of claim 29, further comprising:
admixing a compatibilizing agent into the two-phase system.

54. The method of claim 29 admixing a compatibilizing agent into the two-phase system, the compatibilizing agent comprising an intermixture
30 of hydrophobic and a hydrophilic regions.

55. The method of claim 29, further comprising:

admixing a compatibilizing agent to the two-phase system, the compatibilizing agent comprising a copolymer of a hydrophilic monomer and a hydrophobic monomer.

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56. The method of claim 53, 54 or 55, wherein the compatibilizing agent is admixed into the organic solvent.

57. The method of claim 53, 54 or 55, wherein the compatibilizing agent is admixed into the aqueous suspension.

10

58. The method of claim 53, wherein the compatibilizing agent comprises poly(vinylpyrrolidinone/1-hexadecene).

15

59. The method of claim 53, wherein the compatibilizing agent comprises poly(vinylpyrrolidinone/1-eicosene).

20

60. A method for the manufacture of hydroxypropyl cellulose gel beads, comprising the steps of:

providing an aqueous suspension of hydroxypropyl cellulose, a fine mineral oil as an organic solvent and vinyl sulfone as a crosslinker, where the fine mineral oil organic solvent is immiscible with the aqueous suspension;

admixing the aqueous hydroxypropyl cellulose suspension, the fine mineral oil organic solvent and vinyl sulfone to form a two-phase system; agitating the two-phase system sufficient to form droplets of aqueous hydroxypropyl cellulose suspension in the fine mineral oil organic solvent; maintaining agitation of the two-phase system for a time sufficient to form crosslinked hydroxypropyl cellulose gel beads; and

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recovering the crosslinked hydroxypropyl cellulose gel beads from the fine mineral oil organic solvent.

5 61. The method of claim 60, further comprising:
admixing a compatibilizing agent to the two-phase system.

62. A method of suspension crosslinking comprising:
admixing a compatibilizing agent to a two-phase system, comprising
an aqueous polymer suspension, a crosslinker and an organic solvent, where
10 droplets of the aqueous polymer suspension and the organic solvent comprise
the two phases of the system.

63. A method for the manufacture of responsive gel beads,
comprising:
15 admixing an aqueous suspension, an organic solvent and a crosslinker
to form a two-phase system, where the aqueous suspension and the organic
solvent comprise the two phases of the system;
admixing a compatibilizing agent to the two-phase system;
agitating the two-phase system sufficient to form droplets of the
20 aqueous suspension in the organic solvent;
maintaining agitation of the two-phase system for a time sufficient to
form crosslinked cellulose ether gel beads; and
separating and recovering from the organic solvent crosslinked gel
beads having a diameter of less than or equal to 50 microns as prepared and
25 measured at a temperature of less than 30°C.

64. A responsive gel bead, comprising:
a polymer which is chemically crosslinked with a bi-functional or
multi-functional organic compound, characterized in that the gel bead is
30 capable of absorbing at least 5 grams solvent per milliliter of collapsed gel

in one hour or less, wherein the collapsed gel is at a temperature of no greater than 75°C.

65. A responsive cellulosic gel bead, comprising:

- 5 a cellulose ether polymer which is chemically crosslinked with a bifunctional or multi-function organic compound having a diameter in a collapsed state of less than 600 μm .

66. The gel bead of claim 1, characterized in that the gel bead is
10 capable of absorbing at least 5 grams solvent per millimeter of collapsed gel.

67. The gel bead of claim 1, characterized in that the gel bead is capable of absorbing at least 5 grams solvent per millimeter of collapsed gel in one hour or less.

15

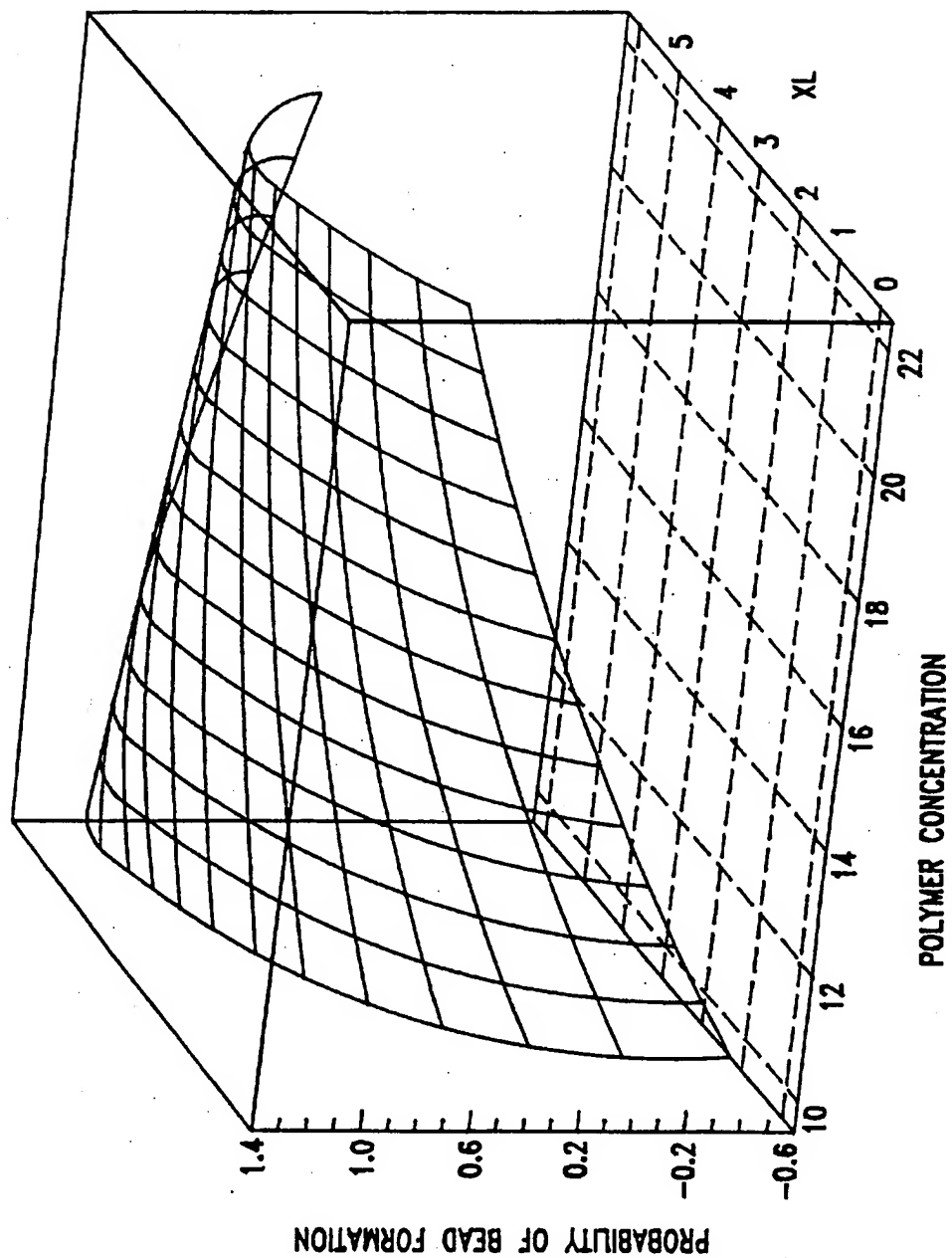
68. The gel bead of claim 1, characterized in that the gel bead is capable of absorbing at least 5 grams solvent per millimeter of collapsed gel in two hours or less.

20

69. The gel bead of claim 1, wherein the ratio of a mean diameter of the gel bead in a collapsed state to a median diameter of the gel bead in a collapsed state is no more than 1.2.

70. The gel bead of claim 1, wherein the gel bead comprises
25 hydroxypropylmethyl cellulose.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/09037

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C08B15/00 C08J3/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C08B C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>APPLIED BIOCHEMISTRY AND BIOTECHNOLOGY, vol. 19, no. 1, October 1988 pages 1-9, T. G. PARK ET AL. 'Effect of temperature cycling on the activity and productivity of immobilized galactosidase in a thermally reversible hydrogel bead reactor' see abstract see page 2, line 12 - line 17 see page 2, line 34 - line 35 see page 3; figure 1</p> <p style="text-align: center;">--- -/-</p>	1

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

16 November 1995

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/09037

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p> DATABASE WPI Week 7812 Derwent Publications Ltd., London, GB; AN 78-22090A & JP,A,50 151 289 (JUJO PAPER MFG KK) , 4 December 1075 see abstract ----- </p>	<p> 29, 30, 32, 33, 39-42 </p>

